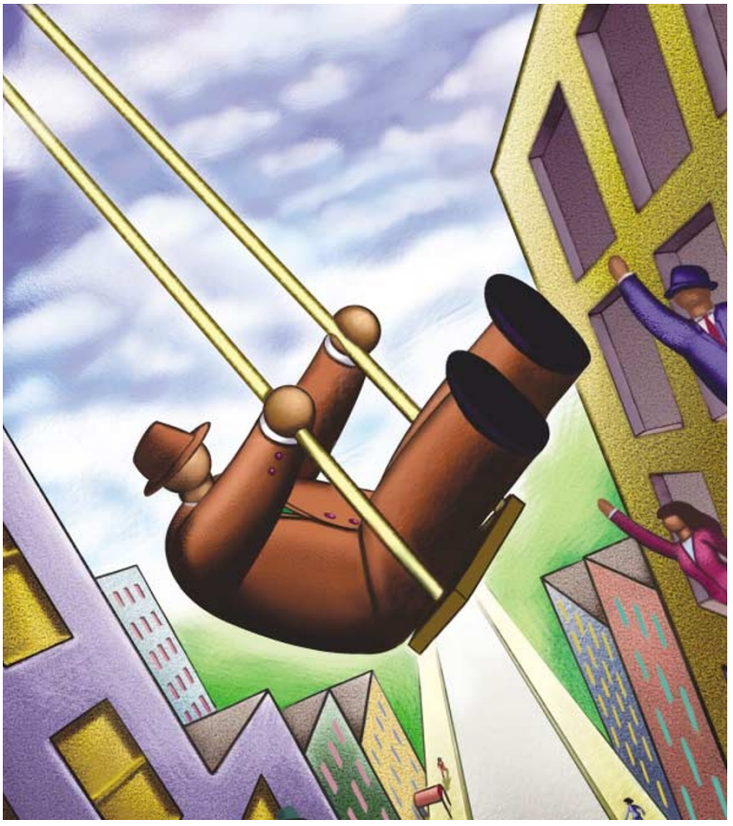

T-CELL DEVELOPMENT

Trapped in adolescence

Immature $CD4^+CD8^+$ double-positive (DP) thymocytes require signals from thymic stromal cells to develop into mature $CD4^+$ or $CD8^+$ single-positive T cells. The exact nature of these signals is unknown, but Tedder and colleagues now report in *Cell* a surprising role for CD83 — a cell-surface molecule of unknown function that is expressed by thymic epithelial and dendritic cells — in $CD4^+$ T-cell development.

To investigate the physiological role of CD83, the authors generated *Cd83*$^{-/-}$ mice. These mice had a specific block in $CD4^+$ T-cell differentiation in the thymus, but developed normal numbers of DP and $CD8^+$ T cells. This defect resulted in a severe reduction in the number of $CD4^+$ T cells in the periphery.

Adoptive-transfer experiments were performed to investigate whether the abnormal $CD4^+$ T-cell development was due to an intrinsic thymocyte defect or to a defect in the thymic microenvironment. *Cd83*$^{-/-}$ thymocytes developed normally when transferred into wildtype mice, whereas wildtype thymocytes failed to differentiate into mature $CD4^+$ T cells in *Cd83*$^{-/-}$ mice. In addition, the transplantation of wildtype epithelial cells into the thymi of *Cd83*$^{-/-}$ mice

INNATE IMMUNITY

Bacterial recognition

An important component of immune responses in *Drosophila* is the activation of antimicrobial peptides in the fat body, which is the equivalent of the mammalian liver. Two signalling pathways control this response — the Toll pathway, which mostly mediates responses against Gram-positive bacteria and fungi, and the Imd pathway, which principally mediates responses against Gram-negative bacteria through activation of the NFκB transcription factor Relish — but the link between infection and activation of these pathways is largely unknown. Recently, the Toll pathway was shown to be activated by Gram-positive bacteria by means of the circulating peptidoglycan recognition protein (PGRP) PGRP-SA. Now, three groups — using different experimental approaches — have identified another PGRP molecule, a membrane molecule PGRP-LC, as a putative receptor for the Imd signalling pathway.

Rämet and colleagues used a functional genomics approach to identify genes that are involved in phagocytosis *in vitro*. Double-stranded RNAs (dsRNAs) were synthesized randomly from a *Drosophila* macrophage S2 complementary DNA library. One thousand dsRNAs were incubated with target S2 macrophages, and the ability of treated cells to phagocytose bacteria was assessed. Fifty-six RNA interference (RNAi) treatments, involving 45 different genes, yielded detectable phenotypes. Of these, one RNAi that targeted membrane-bound PGRP-LC reduced the phagocytosis of Gram-negative *Escherichia coli*, but not Gram-positive *Staphylococcus aureus*. Microarray analysis showed that PGRP-LC RNAi inhibited the production of peptides induced through the Imd pathway in response to *E. coli*. Flies with mutations in *PGRP-LC* were susceptible to *E. coli* infection owing to impaired antimicrobial responses.

Gottar and colleagues used a modified transposon insertion library to look for PGRP mutants and to analyse their effects on the induction of expression of antimicrobial peptides. They identified *PGRP-LC*-mutant flies, which had a severely decreased ability to respond to Gram-negative bacteria, but responded normally to Gram-positive bacteria and fungi. When the transposon element was mobilized, several revertant lines were identified that responded as wildtype flies do to Gram-negative bacteria, and the overexpression of PGRP-LC was sufficient to rescue the *PGRP-LC* mutants. When flies that overexpressed PGRP-LC under the control of a heat-shock promoter were exposed to heat shock, they produced antimicrobial peptides as if they were responding to Gram-negative bacterial infection.

Using a genetic approach, Choe and colleagues identified the *ird7* (immune response deficient 7) gene as a component of the *Drosophila* antimicrobial response. Antimicrobial gene expression in response to bacterial infection in *ird7*-mutant flies was similar to that observed in *imd*- and *Relish*-mutant flies, which suggests that ird7 is a component of the same pathway as Imd and Relish. The *ird7* mutations were mapped to PGRP-LC, and PGRP-LC RNAi was shown to block the expression of antimicrobial peptides in response to *E. coli*, peptidoglycan and lipopolysaccharide.

Together, these three papers support the role of PGRP-LC as a possible pattern-recognition receptor for the Imd signalling pathway. It remains to be determined whether PGRP-LC signals directly to the Imd pathway, or whether a co-receptor is required to initiate signalling (see figure). Four PGRP genes have been identified in the human genome, and it will be interesting to determine the function of these genes in mammalian innate immunity.

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References and links

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